

Claims:

- July 15
1. A method of generating a contrast enhanced image of a human or non-human animal subject which comprises administering to said subject an effective amount of a magnetic resonance imaging contrast agent and generating an image of at least part of said subject containing said agent, wherein said agent comprises a physiologically tolerable lanthanide compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 5, and which is convertible in vivo from said first to said second oxidation state whereby contrast is enhanced in a body region in which conversion to said second state does or does not occur.
2. A method as claimed in claim 1 wherein said agent comprises a physiologically tolerable lanthanide compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 10.
3. A method as claimed in claim 1 wherein said agent comprises a physiologically tolerable lanthanide compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 20.
4. A method as claimed in claim 1 wherein said agent comprises a physiologically tolerable lanthanide compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 100.
5. A method as claimed in any one of claims 1 to 4 wherein the change between said first and said second oxidation states is effected as a change from a

paramagnetic to a diamagnetic state, as a change from a diamagnetic to a paramagnetic state, or as a change between two paramagnetic states of the lanthanide metal ion.

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6. A method as claimed in claim 5 wherein said change between two paramagnetic states is effected as a change from a non-spherically symmetric electronic ground state to a spherically symmetric electronic ground state, or a change from a non-spherically symmetric electronic ground state to a spherically symmetric excited state.

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7. A method as claimed in any preceding claim wherein said agent is a chelate complex of a lanthanide metal ion, or a physiologically tolerable salt thereof.

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8. A method as claimed in any preceding claim wherein said agent is a Europium compound, preferably a chelate complex of Europium or a physiologically tolerable salt thereof.

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9. A method as claimed in claim 8 wherein said Europium compound is activated by switching between the II and III oxidation states of the metal ion.

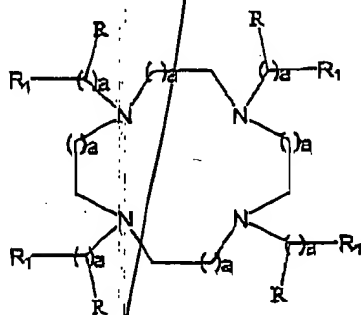
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10. A method as claimed in any one of claims 7 to 9 wherein said chelate complex is a complex of a chelant selected from the group consisting of DTPA, EDTA, DTPA-BMA, DO3A, DOTA, HP-DO3A, TMT and DPDP.

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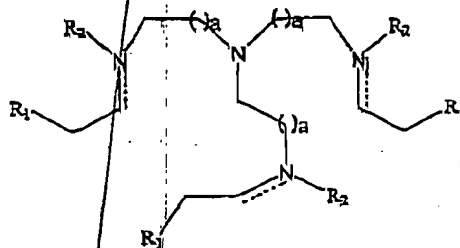
11. A method as claimed in any one of claims 7 to 9 wherein said chelate complex is a complex of a chelant selected from the group consisting of porphyrins and porphyrin-like molecules, phthalocyanines, crown ethers, hemin, heme, chelants having a square planar symmetry, cryptands and cryptates.

12. A method as claimed in any one of claims 7 to 9 wherein said chelate complex is a complex of a chelant selected from compounds of formulae (I), (II), (III), (IV), (V) and (VI):



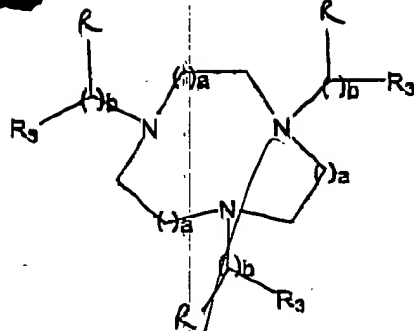
(I)

where each a independently represents an integer between 1 and 3, each R independently represents hydrogen or hydroxy and each R₁ independently represents a carboxylate, phosphate, thioacid, thiol, amino alkoxide or hydroxy group;



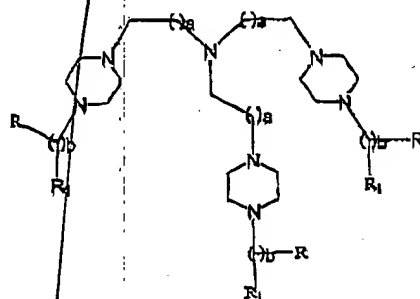
(II)

where a and R₁ are as hereinbefore defined and each R₂ independently represents hydrogen, C₁₋₆ alkyl or aryl, with the proviso that R₂ is absent when the double bond is present on the same nitrogen;



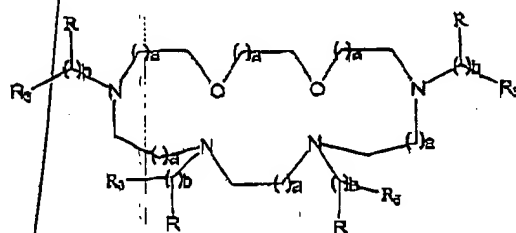
(III)

where a , R and R_2 are as hereinbefore defined, b is an integer between 0-3 and each R_3 independently represents R_1 , $NR-NR_2-COO^*$, or $N=N-COO^*$ when b is positive or each R_3 independently represents $N=CH-COO^*$ or $NR_2-CH_2-COO^*$;



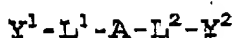
(IV)

where a , b , R and R_1 are as hereinbefore defined;



(V)

where a , b , R and R_3 are as hereinbefore defined;



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(VI)

where A is N, CR₄, E, P=O, cis,cis,cis-1,3,5-trisubstituted-cyclohexane or an N,N',N''-trisubstituted-triaza 9 to 14 membered macrocyclic ring;

L¹, L², L³ are linker groups which are independently chosen from C₁₋₄ alkylene, C₄₋₈ cycloalkylene or C₄₋₈ o-arylene;

Y¹, Y², Y³ are independently chosen from -NH₂, -B(=O)OZ, -N=CR₅-B(=O)OZ, -NR₅-CR₆-B(=O)OZ, -N[CR₆-B(=O)Q]₂ and -O-CR₆-B(=O)OZ where B is C or PR₆, each Q is independently -OZ or -NR₆, and Z is H or a counter-ion;

each R₄ and R₅ group is independently chosen from H, C₁₋₅ alkyl, C₁₋₅ alkoxyalkyl, C₁₋₅ hydroxyalkyl, C₁₋₅ aminoalkyl, C₅₋₁₀ aryl or C₁₋₆ fluoroalkyl;

R₆ is OH, C₁₋₆ alkyl, C₁₋₆ alkoxyalkyl, C₁₋₆ fluoroalkyl, C₁₋₁₀ alkoxy or C₅₋₁₀ aryl;

with the proviso that at least one of Y¹, Y² and Y³ is -N=CR₅-B(=O)OZ.

13. A method as claimed in any preceding claim wherein said agent is conjugated to a biological vector capable of targeting said agent to a desired region of the body.

14. A method as claimed in claim 13 wherein said biological vector is selected from the group consisting of an antibody, an antibody fragment and an oligopeptide binding motif.

15. A method as claimed in any preceding claim wherein conversion between said first and second oxidation states is effected in vivo by a localised normal or

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abnormal biological process, by an administered chemical agent or by illumination of said agent with light.

5 16. A method as claimed in claim 15 wherein conversion between said first and second oxidation states is effected in vivo by the presence or absence of oxygen or of oxidation or reduction promoting agents, from a change in temperature or as a result of an increase or decrease in pH at the target site, or as a result of the
10 presence of a specific enzyme.

15 17. A method as claimed in claim 15 wherein said chemical agent is a redox reagent capable of delivery to or accumulation at a desired target site within the body.

20 18. A method as claimed in claim 15 wherein conversion between said first and second oxidation states is effected by application of light having a wavelength of from 600 to 1300 nm.

25 19. An MR contrast agent composition comprising as an MR contrast agent a physiologically tolerable lanthanide compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 5, and which is convertible in vivo from said first to said second oxidation state whereby contrast is enhanced in a body region in which
30 conversion to said second state does or does not occur, together with an optionally encapsulated physiologically tolerable trigger substance capable of converting said contrast agent between said first and second oxidation states.

35 20. A composition as claimed in claim 19 wherein said trigger substance is an enzyme, a redox agent or a free radical scavenger.

21. The use of a physiologically tolerable MR contrast agent substance comprising a physiologically tolerable lanthanide compound or salt thereof having first and second oxidation states which differ in relaxivity by a factor of at least 5, and which is convertible in vivo from said first to said second state whereby contrast is enhanced in a body region in which conversion to said second state does or does not occur, for the manufacture of a diagnostic contrast medium for use in a method of diagnosis involving image generation according to a method as claimed in any one of claims 1 to 18.

22. Use as claimed in claim 21 for the manufacture of a diagnostic contrast medium for use in a method of detecting malignant melanoma, squamous cell carcinoma, sarcomas or adenocarcinomas.

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